Claims 1, 3, 5, 6, 14, and 20 are amended herein. The amendments are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter. In particular, Claims 1 and 14 are amended to recite "isolated hepatic progenitors." Support for this amendment is found throughout the specification as filed and particularly at page 8, line 18. Claim 3 is amended to provide context of comparison for expression of MHC class Ib antigen by cells of the claimed invention. Support for this amendment is found at page 12, line 23, to page 13, line 4, and particularly at Tables 4 and 5 on page 26. Claims 5, 6, and 14 are amended to recite "of the same species," as suggested by Examiner. Claim 14 is amended to remove reference to weakness of expression of MHC class Ib antigen as shown by dull positive response to immunostaining. This limitation is removed to Claim 20, which is also amended to provide context of comparison for expression of MHC class Ib antigen by cells of the claimed invention. Support for this amendment is found at page 12, line 23, to page 13, line 4, and particularly at Tables 4 and 5 on page 26. Claim 14 is also amended to recite "the hepatic progenitors are capable of differentiation." This amendment finds support throughout the specification as filed, as particularly at Claim 1, as filed.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Office Action, at pages 4-6, rejects Claims 1-20 as allegedly being anticipated by Haruna *et al.* (Hepatology, 23:476-481, 1996)(hereinafter, "Haruna") under 35 U.S.C. § 102(b). The Examiner is of the opinion that since Haruna *et al.* allegedly teach the

isolation and identification of bipotent liver progenitor cells from human fetal livers, and that the allegedly isolated cells would reasonably be expected to have the same physical and biochemical properties as the cells of Applicants' invention as claimed. Applicants respectfully traverse.

Applicants submit respectfully that the claims of the present invention, as amended, are not anticipated by Haruna. As Examiner is no doubt well aware, in order to anticipate a claimed invention, a cited reference must explicitly or inherently disclose each and every limitation of the claimed invention. Independent Claims 1 and 14, as amended, include the limitation that the bipotent hepatic progenitor cells of the present invention have the ***capacity to differentiate***. Without acquiescing in propriety of Examiner's argument that the identified cells of Haruna are bipotent hepatic progenitor cells, Applicants respectfully draw Examiner's attention to Haruna, for example on page 476, wherein Haruna teaches immunoperoxidase staining of ***formalin-fixed paraffin sections*** of fetal, infant, and adult livers with monoclonal and polyclonal antibodies in order to detect the presence and characteristics of putative bipotent hepatic progenitors. Applicants' submit respectfully that, as one skilled in the art will immediately recognize, mammalian liver cells that have been subjected to formalin fixation, and that are subsequently contained within peroxidase-stained paraffin sections, are no longer viable. Hence, such cells are not capable of differentiation as required under Claims 1 and 14, as amended. Accordingly, Applicants submit respectfully that the cells of Haruna cannot anticipate Applicants' claimed invention, and Applicants request respectfully that the rejection to Claims 1-20 under 35 U.S.C. § 102(b) be withdrawn.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

At pages 2-4 of the Office Action, Claims 3, 5, and 14-20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention.

In particular, at page 3 of the Office Action, the prior rejection of Claims 3 and 14 with regard to the recitation of the term "weakly" is maintained. The Office Action alleges that the claims are unclear because they recite the term "dull positive response to immunostaining," and it is allegedly unclear what the metes and bounds of weak expression are because weak expression is defined by "dull positive" and the term "dull" is not specifically defined. Applicants traverse respectfully.

Without acquiescing in the propriety of the rejection, Applicants herein amend Claim 14 to remove recitations of and references to the terms "weakly" and "dull positive" so that the claim now recites that the cells "express MHC class Ib antigen." Accordingly, Applicants submit respectfully that the rejection of Claim 14 as allegedly unclear is rendered moot, and Applicants respectfully request that the rejection of Claim 14 under 35 U.S.C. § 112, second paragraph, be withdrawn.

With regard to the rejection of Claim 3, noted above, Applicants submit respectfully that Claim 3, as amended, is not unclear with respect to the recitation of the terms "weakly" and "dull positive." Without acquiescing in the propriety of the rejection, Applicants herein amend Claim 3 to recite that the expression of MHC class Ib antigen is weak in comparison to expression of ICAM as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody in comparison to a positive response to immunostaining with anti-ICAM

antibody. As defined at page 12, line 23, to page 13, line 4, a dull positive response is an empirically-determined value determined with respect to other antigens, a dull positive response being lower in emitted fluorescent light intensity than a bright-fluorescing positive response. As noted throughout the specification as filed, and particularly at Tables 4 and 5 on page 26, hepatic progenitor cells of the present invention have a positive immunostaining response to ICAM. Hence, Applicants submit respectfully that the dull positive response to immunostaining of MHC class Ib antigen may be empirically determined in comparison to the positive response to immunostaining for ICAM in the same cells. Accordingly, Applicants submit respectfully that the rejection of Claim 3 under 35 U.S.C. § 112, second paragraph, has been overcome, and Applicants request respectfully that the rejection of Claim 3 be withdrawn.

The Office Action, at page 3, rejects Claim 5 as unclear because the metes and bounds of the comparison between flow cytometrically-determined side-scatter values (SSC) of hepatic progenitors to mature parenchymal cells are allegedly not specifically defined. Likewise, the prior rejection of Claim 14 is maintained at page 4 of the Office Action, where the Office Action alleges that Claim 14 is unclear for recitation of the term "higher" with regard to a comparison of the SSC value of hepatic progenitors and their progeny to non-parenchymal cells, as the metes and bounds of the comparison between the hepatic progenitor cells and the non-parenchymal cells are allegedly not specifically defined. The Office Action, for example, asks the question, "are the hepatic progenitors from a different animal species than that of the non-parenchymal cells?" Applicants traverse respectfully.

Applicants respectfully direct Examiner's attention to page 9 of the specification as filed, lines 8-11, which disclose that SSC is a measure of cell granularity and cytoplasmic lipid droplet

content, and that hepatic precursors have an SSC value that is higher than the SSC value for non-parenchymal cells but lower than that for mature parenchymal cells. Without acquiescing in the propriety of the rejection, Applicants herein amend Claims 5 and 14 to recite "of the same species" with regard to the comparison of SSC values of hepatic progenitors to mature or non-parenchymal cells. Thus, Applicants submit respectfully that Claims 5 and 14 are not unclear, and Applicants request respectfully that the 35 U.S.C. § 112, second paragraph, rejection of Claims 5 and 14 be withdrawn.

The Office Action, at pages 3-4, also rejects Claim 15 as allegedly unclear for the recitation that the hepatic progenitors, their progeny, or a combination are derived from endoderm or bone marrow. The Office Action alleges that it is unclear what the term "derived from" encompasses because the metes and bounds of the term are not specifically defined. Applicants traverse respectfully.

Respectfully, Applicants draw Examiner's attention to page 8, line 18, to page 9, line 4, of the specification as filed, which teaches that the present invention, as claimed, is directed to the isolation of hepatic progenitors from endodermal or bone marrow tissue, the clonal growth of the hepatic progenitors, and compositions containing the hepatic progenitors. Cells isolated from endoderm or bone marrow are "derived from" those tissues in the sense of having their origin in those tissues. However, the clonal growth of hepatic progenitors may occur *ex vivo* from mother cells either having been extracted from tissue or taken from another cell culture to produce daughter cells that were not extracted from tissue, and compositions containing hepatic progenitors may exist *ex vivo* and contain hepatic progenitors that were extracted from tissue or were grown from extracted or non-extracted mother cells in culture. Claim language should be

construed as broadly as possible in order to provide Applicants with the broadest claim scope allowable. Thus, the term "derived from endoderm or bone marrow," as used in the present invention, as claimed, should be construed as meaning both "taken or isolated from endodermal or bone marrow tissue" or "having an ancestry including a mother cell that originated in endoderm or bone marrow."

In response to Examiner's suggestion that the claims of the present invention read upon an intact liver, Applicants have amended Claims 1 and 14 herein to recite "isolated hepatic progenitors."

In view of the foregoing, Applicants suggest respectfully that the 35 U.S.C. § 112, second paragraph, rejections of Claims 3, 5, and 14-20 have been traversed, and Applicants request respectfully that the 35 U.S.C. § 112, second paragraph, rejections of Claims 3, 5, and 14-20 be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,

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Dated: February 26, 2003

EXHIBIT A

MARKED-UP VERSION OF THE CLAIMS
U.S. PATENT APPLICATION NO. 09/678,953

1. (Twice Amended) A composition comprising isolated bipotent hepatic progenitors which express at least one intercellular adhesion molecule (ICAM) antigen and do not express major histocompability complex (MHC) class Ia antigen, in which the bipotent hepatic progenitors have a capacity to differentiate.

3. (Twice Amended) The composition of Claim 2 in which the MHC class Ib antigen is weakly expressed in comparison to expression of ICAM as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody in comparison to a positive response to immunostaining with anti-ICAM antibody.

5. (Twice Amended) The composition of Claim 1 in which the hepatic progenitors have a sidescatter value determined by flow cytometry which is numerically less than the sidescatter value of mature parenchymal cells of the same species.

6. (Once Amended) The composition of Claim 1 in which the hepatic progenitors have a sidescatter in flow cytometry which is between the sidescatter of nonparenchymal cells of the same species and the sidescatter of mature parenchymal cells of the same species.

14. (Twice Amended) A composition comprising isolated hepatic progenitors, their progeny, or a combination thereof in which the hepatic progenitors and their progeny:

(a) [weakly] express[, as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody,] at least one MHC class Ib antigen;

(b) exhibit a numerically higher sidescatter value determined by flow cytometry than the sidescatter value of nonparenchymal cells of the same species; [and]

(c) express alpha-fetoprotein, albumin, CK 19, or combinations thereof; and

(d) wherein the hepatic progenitors are capable of differentiating.

20. (Once Amended) The composition of claim 15 in which the progenitors weakly express at least one MHC class Ib antigen in comparison to expression of ICAM as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody in comparison to a positive response to immunostaining with anti-ICAM antibody.

PENDING CLAIMS AS OF AMEND. C, #17
priority 10/1/99

MARKED-UP VERSION OF CLAIMS SHOWING CHANGES MADE

1. (Twice Amended) A composition comprising isolated bipotent hepatic progenitors which express at least one intercellular adhesion molecule (ICAM) antigen and do not express major histocompability complex (MHC) class Ia antigen, in which the bipotent hepatic progenitors have a capacity to differentiate.

C1

2. The composition of claim 1 in which the hepatic progenitors express at least one MHC class Ib antigen.

3. (Twice Amended) The composition of Claim 2 in which the MHC class Ib antigen is weakly expressed in comparison to expression of ICAM as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody in comparison to a positive response to immunostaining with anti-ICAM antibody.

C2

4. The composition of claim 1 in which the ICAM antigen is ICAM-1.

5. (Twice Amended) The composition of Claim 1 in which the hepatic progenitors have a sidescatter value determined by flow cytometry which is numerically less than the sidescatter value of mature parenchymal cells of the same species.

C3

6. (Once Amended) The composition of Claim 1 in which the hepatic progenitors have a sidescatter in flow cytometry which is between the sidescatter of nonparenchymal cells of the same species and the sidescatter of mature parenchymal cells of the same species.

cont

7. The composition of claim 1 in which the hepatic progenitors are capable of dividing and giving rise to progeny.

8. The composition of claim 7 in which the hepat[illegible]nitors exhibit a capacity for clonal growth.

9. The composition of claim 8 in which the clonal growth requires extracellular matrix.

10. The composition of claim 7 in which the progeny grow in piled-up clusters.

11. The composition of claim 7 in which the progeny express alpha-fetoprotein, albumin, CK19, or combinations thereof.

12. The composition of claim 7 in which the progeny are hepatocytes or biliary cells.

13. The composition of claim 12 in which the hepatocytes or biliary cells additionally express a cell adhesion molecule that can be used for selection or identification of a particular subpopulation.

14. (Twice Amended) A composition comprising isolated hepatic progenitors, their progeny, or a combination thereof in which the hepatic progenitors and their progeny:

(a) express at least one MHC class Ib antigen;

C4 (b) exhibit a numerically higher sidescatter value determined by flow cytometry than the sidescatter value of nonparenchymal cells of the same species;

(c) express alpha-fetoprotein, albumin, CK 19, or combinations thereof; and

(d) wherein the hepatic progenitors are capable of differentiating.

15. The composition of claim 14 in which the hepatic progenitors, their progeny or a combination thereof are derived from endoderm or bone marrow.

16. The composition of claim 15 in which the endoderm is selected from liver, pancreas, lung, gut, thyroid, gonad, or combinations thereof.

B-cell islet cells

17. The composition of claim 15 in which the progenitors express ICAM antigen.

18. The composition of claim 17 in which the ICAM antigen is ICAM-1.

19. The composition of claim 15 in which the progenitors do not express MHC class Ia. (classical)

20. (Once Amended) The composition of Claim 15 in which the progenitors weakly express at least one MHC class Ib antigen in comparison to expression of ICAM as indicated by a dull positive response to immunostaining with fluorescent anti-MHC class 1b antibody in comparison to a positive response to immunostaining with anti-ICAM antibody.